REMARKS

Amendments to the claims previously introduced by a Supplemental Amendment taking into account the discussion between the Examiner and the undersigned during the telephonic interview of February 4, 2010 have been entered and considered. On this basis, the rejection of the claims as anticipated by Dalemans has been withdrawn, which Applicant gratefully acknowledges. The claims are now rejected as obviousness over Dalemans taken with a secondary reference (Volkin) discussed further below. Applicant respectfully requests reconsideration of the presently claimed invention in view of the remarks below.

Rejection under 35 U.S.C. § 103(a)

Claims 1-6 and 8-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dalemans, et al. (WO 99/30733, published June 24, 1999) in view of Volkin, et al. (WO 00/02591, published January 20, 2000).

Basis of the rejection

The Examiner's position in respect of Dalemans, which are on record from the previous Office Actions, is reiterated. In brief, the examiner indicates that Dalemans teaches compositions comprising a DNA component and a protein component (which comprises preferably the same immunodominant epitope as encoded by the DNA component). Upon administration, a synergistic effect occurs, in the sense that the protein component enhances the efficacy of the DNA component. Moreover, according to the examiner, Dalemans teaches prior mixing of the protein with an adjuvant. In addition, the examiner cites Dalemans that the combination of DNA and protein components exhibits a more balanced Thl + Th2 response.

In respect of Volkin, the examiner states that negatively-charged mineral-based adjuvants (such as aluminium phosphate) in combination with DNA vaccine components are taught. Moreover, according to the examiner, such adjuvated DNA vaccines increase the immune response.

According to the examiner, it would have been obvious for a person skilled In the art to combine the teachings of Dalemans and Volkin to come the present invention. According to the examiner, it would have been obvious to modify the composition as used in Dalemans to include

a negatively-charged mineral-based adjuvant, as taught by Volkin with reasonable expectation of success as such composition would have yielded a predictable and synergistic result.

Rebuttal

Applicant asserts that one of ordinary skill in the art would have no incentive to combine the teachings of Dalemans and Volkin with a reasonable expectation of success on the one hand, while on the other hand if one would combine the teachings of Dalemans and Volkin, such would not lead to the present invention.

The present invention

The present invention relates to vaccine compositions comprising a polynucleotide vaccine component, a protein antigen vaccine component and a negatively charged mineral based adjuvant. The vaccine compositions are characterized in that the negatively charged mineral-based adjuvant is **pre-incubated with the protein antigen** vaccine component prior to formulating with the polynucleotide vaccine component. This results on the one hand in a vaccine with a different appearance (see p.6, 1.21-25 of the application as filed) and on the other hand (as a consequence) in a vaccine capable of differentiating the immune response with regard to the Th1 and Th2 response, but not in the sense that you get a mixed Th1/Th2 response to each of the vaccine components (DNA and protein), but instead a non-discriminatory Th-1 and Th-2 response. In particular, the present invention enables the user to stimulate either or both a Th-1 and Th-2 response in the sense that it enables the user to **predetermine** towards which antigen you want a Th-2 response (the component added as the protein antigen adsorbed onto the negatively charged mineral adjuvant, see Figure 1 of the present application) and concomitantly - in the same vaccine formulation - towards which antigen you want a Th-1 response (the component added as a DNA polynucleotide). The present invention does not relate to simply enhancing the (pre-existing) immunological response of the DNA vaccine component, in contrast to the cited prior art.

Dalemans does not relate to differentiating and pre-determining the immunological response

The examiner asserts that Dalemans reports an enhanced and differentiated immunological response.

While Dalemans indeed reports a more balanced Th1/Th2 response (p.7, 1.14-16 of Dalemans), such is not supported by the experimental data in Dalemans.

In particular, Dalemans attempts to enhance the low inherent efficacy of DNA vaccines (**Thl response**) by combining it with a protein vaccine to enhance the immunological response of the DNA vaccine (p4, 1.10-11 of Dalemans). Dalemans states that the presence of such protein (polypeptide) has been found to actually **enhance the efficacy of the DNA vaccine** (p4, 1.10-11 of Dalemans). Indeed, claim 13 of Dalemans is directed to a method to enhance a Th1 immune response by administering a vaccine composed of a DNA and a protein antigen component. This notion is In fact also acknowledged by the examiner (see page 5, first paragraph of the present Office Action).

The examples of Dalemans show the same. Examples 1 and 2 merely describe vaccine preparation and immunization protocols. In Example 3, DNA vaccination leads to a strong Thl immunological response (IgG2a), whereas protein vaccination has a complete bias for the opposite, which is a Th2 response (IgGl). The mixed DNA/protein vaccination leads also to a Thl response, but not to a combined Thl/Th2 response (see p.18, 1.5-9 of Dalemans; cf. Example 4, p.20, 1.23-28; Example 5, p.22, 1.4-6 of Dalemans). In Example 7, the DNA component is administered prior to the protein component. Again, an increased Thl immunological response (IgG2a) is shown (Figure 5: p.23, 1.23-26; Figure 6: p.23, 1.28-30 of Dalemans). No adjuvants were added to the vaccine compositions in any of the above examples.

Examples 8 and 9 describe delayed-release formulations (cf. p.24, 1.27-28 of Dalemans). For this purpose, the protein antigen is premixed with a positively-charged mineral-based adjuvant (i.e. aluminium hydroxide) supplemented with a second adjuvant, polycaprolactone (cf. p.24, 1.5-7 of Dalemans), creating a slow-release protein antigen component (p.24, 1.16-19 of Dalemans). Subsequently, but prior to immunization, the DNA component was added. Allegedly, this form of immunization leads to an increased overall immunological response, comparable to Example 7 of Dalemans, *i.e.* a Thl response.

Thus, the combination vaccine of a DNA component and a protein antigen leads always to a Thl response, irrespective of adjuvants.

In this respect, it appears that the examiner incorrectly combines different experimental setups (Example 4 on the one hand and Examples 8 and 9 on the other hand) to come to the conclusion that Dalemans would teach a differentiated (i.e. Thl and Th2) response. The examples given in Dalemans represent consecutive experiments, where the teachings of the previous example are implemented in the next example.

Moreover, only Examples 8 and 9 refer to the use of an adjuvant, but only positively charged mineral-based adjuvants. No negatively charged adjuvants have actually been used. Dalemans is completely silent regarding the difference in effects of positively or negatively charged mineral-based adjuvants. The addition of an adjuvant is optional and is certainly not a key component in the teachings of Dalemans.

Volkin does not relate to differentiating and pre-determining the immunological response.

Volkin likewise does not relate to differentiating the immunological response. In particular, Volkin attempts to **increase the low inherent efficacy of DNA vaccines** by combining it with a negatively charged mineral-based adjuvant (p.4, 1.22-24 of Volkin). The function and effect of the adjuvant as described by Volkin is not to differentiate the immunological response. Indeed, Example 3 (Table 3 and p.27, 1.4-9 of Volkin) teaches that coadministration of a DNA vaccine with a negatively charged aluminium phosphate adjuvant does not result in a qualitative difference in the isotypes of antibody produced, i.e. the dominant antibody isotype is both after vaccination with or without adjuvant IgG2a, indicative of a Thl immunological response (c.f. above). In other words, a negatively charged mineral-based adjuvant does not serve the purpose of differentiating an immunological response.

Thus, Volkin teaches that a negatively charged mineral-based adjuvant leads to an enhanced Thl immunological response, but does not differentiate the immunological response.

Combining Dalemans and Volkin does not lead to the invention

First, both Dalemans and Volkin teach that DNA vaccination leads to a Thl response, irrespective of additional components in the vaccine, such as protein antigens or adjuvants. Therefore, the person skilled in the art would not have any reasonable expectation of success to solve the problem of **differentiating** and **pre-determining** the immunological response by combining the teachings of Dalemans and Volkin.

Second, the person skilled in the art would have no motivation to combine Dalemans and Volkin to solve the problem, since both relate at best to an enhanced but not to a differentiated and pre-determined immune response.

Third, even if it is accepted that both documents would be combined (which we deny), then this combination would still not lead to the present Invention.

Dalemans teaches the person skilled in the art to combine a protein antigen with a DNA component to prepare a vaccine. Volkin teaches a person skilled in the art to combine a DNA component with a negatively charged mineral-based adjuvant. Hence, the teachings of Dalemans and Volkin combined would lead a person skilled in the art to prepare a vaccine by mixing a DNA component with a negatively charged mineral-based adjuvant and adding a protein antigen. Please note that the order of mixing is not implied in the combined teachings of these two documents. The person skilled in the art would further acknowledge that such a combination at best might enhance the immunological response elicited by the DNA component (a Thl response), but certainly not differentiate the response (a Thl and Th2 response), let alone allow to predetermine the immunological response to the DNA and protein components of the vaccine formulation.

This is, in contrast with the invention described in the present application, a protein antigen is premixed with a negatively charged mineral-based adjuvant to which a DNA component is added. Neither Dalemans nor Volkin teach the composition of part (a) of Applicants' independent claims 1 and 10. The functional effect of such a composition is a differentiated immunological response, *i.e.*, a (1) combined and (2) pre-determined Thl and Th2 response.

Moreover, there is no teaching or suggestion to:

(1) **replace** the positively charged mineral-based adjuvant from Dalemans with a negatively charged mineral-based adjuvant;

(2) **remove** the negatively charged mineral-based adjuvant from the DNA component from Volkin; and

(3) the order of **mixing**.

Accordingly, the references taken as a whole, do not teach all of the elements of the claimed invention.

Neither Dalemans nor Volkin disclose or even give a hint towards the effect of specifically a negatively-charged mineral-based adjuvant into differentiating and predetermining the immunological response towards the protein component and DNA component. In fact, Dalemans uses the same immunodominant epitope for both the protein component as the DNA component. First, such compositions do not allow discriminating to which component the response is elicited. Second, such compositions merely underscore the fact that Dalemans intends to enhance the immunological response towards the DNA component by using the protein as an adjuvant (i.e. to boost the response to the DNA component).

If one would rely on the teachings of Dalemans and Volkin to come to the invention of the present application, one would end up with one of the following alternatives:

a) a vaccine composition with **premixed** protein and adjuvant (which may be negatively charged according to Volkin), **but slow release** formulation (as taught by Dalemans); or

b) a vaccine composition which is **not a slow release** formulation, **but without premixing** protein and adjuvant.

Neither of these options however would result in the subject-matter of the present invention.

Furthermore, the Examiner appears to maintain her position that Dalemans teaches pre-mixing of the protein component with an adjuvant. Applicants again stress that the only reason for premixing in Dalemans is to create a **slow-release** protein component.

Conclusion

The following conclusions can be drawn:

a) Dalemans does not recognize the difference between positively and negatively charged mineral-based adjuvants. As far as Dalemans is concerned, both types are equally suitable. In the present invention however, the necessity of specifically a negatively charged mineral-based adjuvant is recognized for (1) differentiating and (2) pre-determining the immunological response. There is an essential difference between the effects brought about by a positively charged adjuvant and a negatively charged adjuvant, not only regarding the interaction with DNA but also with protein which is not taught by either Dalemans nor Volkin. In this respect, see the graph on page 6 of Applicants' pre-grant publication US 2005/0129712 or page 12 of the Application as filed or page 9 of the Response filed January 21, 2010.

b) Related to the above, Dalemans only includes a positively charged mineral-based adjuvant in a slow release formulation of the protein vaccine component. Such formulation prevents direct contact of the adjuvant with the DNA and thus excludes detrimental effects of the adjuvant in respect of the transcription of the DNA encoded antigen.

c) Volkin does not recognize either the importance of negatively charged adjuvants in respect of pre-determining and differentiating the immunological response. Volkin merely illustrates that negatively charged adjuvants enhance the existing immunological response towards DNA vaccines. However, in the present invention, the adjuvant is combined with the protein component of the vaccine, prior to adding the DNA component (see present claims 1 and 10).

In view of Applicants' arguments, reconsideration and withdrawal of this ground of rejection are respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are

not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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